DOCKET NO.: ISIS-5300 **PATENT**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: **Brenda F. Baker, *et al.***	Confirmation No.: **7033**
Serial No.: **10/701,265**	Group Art Unit: 1635
Filing Date: **November 4, 2003**	Examiner: **Terra C. Gibbs**

For: **Chimeric Oligomeric Compounds And Their Use In Gene Modulation**

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Commissioner:

APPELLANT'S BRIEF PURSUANT TO 37 C.F.R. § 41.37

This brief is being filed in support of Appellant's appeal from the rejections of claims 120, 121, 124, 127 and 136-138 dated April 12, 2011. A Notice of Appeal was filed on September 30, 2011.

1. REAL PARTY IN INTEREST

The real party in interest is the assignee of record for this application, Isis Pharmaceuticals, Inc., 1896 Rutherford Road, Carlsbad, CA 92008.

2. RELATED APPEALS AND INTERFERENCES

Application No. 10/701,264--appeal brief filed March 22, 2012.

Application No. 10/701,236—appeal brief filed April 5, 2012.

Application No. 11/054,848—appeal brief filed April 30, 2010

Application No. 10/701,007—appeal brief filed April 28, 2010

Application No. 10/860,265—appeal brief filed April 30, 2010

3. STATUS OF CLAIMS

Rejected: claims 120, 121, 124, 127 and 136-138

Allowed: none

Withdrawn: none

Objected to: none

Canceled: claims 1 to 119, 122, 123, 125, 126, 128-135 and 139-167.

Appealed: claims 120, 121, 124, 127 and 136-138

4. STATUS OF AMENDMENTS

No claim amendments were made after the rejection of April 12, 2011.

5. SUMMARY OF CLAIMED SUBJECT MATTER

The following summary is for the purpose of complying with the provisions of 37 C.F.R. § 41.37(c)(1)(v). The entire disclosure should be reviewed to obtain a complete understanding of the claimed subject matter.

Claim 120

Claim features	Exemplary description in the specification
A composition comprising a duplex consisting of a first chemically synthesized oligonucleotide and a second chemically synthesized oligonucleotide, wherein:	[0023]
each of the first chemically synthesized oligonucleotide and the second chemically synthesized oligonucleotide independently	[0132], [0133], [0134]

consists of 17 to 25 linked nucleosides, each nucleoside comprising a nucleobase and a sugar;	
the first chemically synthesized oligonucleotide is 100% complementary to the second chemically synthesized oligonucleotide and to a target mRNA;	[0023], [0140]
the first chemically synthesized oligonucleotide and the second chemically synthesized oligonucleotide are not covalently linked to each other; and	[0278], [0279]
the first chemically synthesized oligonucleotide is a gapmer, wherein the gap comprises at least 4 nucleosides, each comprising a 2'-hydroxy-pentofuranosyl sugar moiety, and wherein each nucleoside of each wing comprises a 2'-sugar modification; and	[0025], [0037], [0056], [0336]
the second chemically synthesized oligonucleotide comprises at least one nucleoside that comprises a 2'-sugar modification.	[0194], [0195]

6. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Claims 120, 121, 124, 127, and 136-138 stand rejected under 35 U.S.C. 103(a) as being obvious over Wyatt *et al.* (Nucleic Acids Research 1989, val. 17, pages 7833-7842), Manche *et al.* (Molecular and Cellular Biology 1992), Mania, *et al.* (1993, J. Bio. Chem. v.268:14514-22), and Shibahara, *et al.* (European Patent Application 0339842, published on 11 /02/1989).

7. ARGUMENT

1. Legal principles

As set forth in *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1741 (2007):

> [A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art. Although common sense directs one to look with care at a patent application that claims as innovation the combination of two known devices according to their established functions, it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does.

Thus, it is impermissible to use the claimed invention as an instruction manual or "template" to piece together the teachings of the prior art so that the claimed invention is rendered obvious. *See In re Fritch*, 972 F.2d 1260, 1266 (Fed. Cir.1992).

2. Analysis

Before reviewing the pending obviousness rejection, the Board should appreciate that this application has been pending since November, 2003. In the ensuing eight years, claims in this, and related applications, have been serially rejected under 35 U.S.C. §§ 112, 101, 102, and most recently, 103. Appellants have repeatedly replied at great expense to office action after office action, overcoming one set of rejections, only to be confronted with a new set. In response to the previous rejections under 35 U.S.C. § 103, applicants provided a Declaration from Dr. David Corey, a noted scientist who has been active in the field since the time of the original filing. That Declaration sets forth in detail the factual basis for why one of skill in the art would not have found the claimed oligomeric compounds obvious. The examiner dismissed this declaration, however, simply labeling it non-persuasive. Hoping at long last to resolve this application, applicants then appealed to the Board of Patent Appeals and Interferences and submitted a request for a pre-appeal brief conference that also sets forth in detail why the claimed oligomeric compounds would not have been obvious at the time of the invention. After the notice of appeal and request for a pre-appeal brief conference were filed, rather than allowing

the claims, or even allowing the application to proceed to appeal to finally resolve the outstanding issues, the examiner instead re-opened prosecution, with allegedly "new" grounds for once again rejecting the claims as obvious. The present rejections rely on several references already addressed by appellants and discussed by Dr. Corey. Those previously discussed references are now combined with new, largely duplicative references, not previously cited throughout the long prosecution history of this application. As explained below, these "new" rejections fail for the same fundamental reason as the previous obviousness rejections: the examiner has still not provided a reason why one of skill in the art would have made the claimed compounds prior to invention by the applicants.

a. The applied references considered individually or together do not suggest the claimed subject matter as a whole.

Specifically, those of ordinary skill in the art would not have had any reason to design and produce the claimed oligonucleotides before applicants' invention in view of the description provided in the cited references and the state of the art at that time. Specifically, those of ordinary skill in the art would not have had a reason at the time of the invention to produce duplexes of fully complementary oligonucleotides consisting of 17 to 25 linked nucleosides in which the first oligonucleotide is a gapmer having 2'-modified wings and the second oligonucleotide comprises at least one 2'-sugar modification, in view of the description provided in the cited references.

The Wyatt article describes duplexes of complementary 14-mer oligoribonucleotides, and also describes 14-mer oligoribonucleotide duplexes in which one or two 2'-deoxyribonucleotides were substituted for the ribonucleotides in one or both of the strands. The duplexes were used in *in vitro* experiments for determining the structural requirements of RNase V1. In these experiments, the oligoribonucleotide duplexes and deoxy-substituted duplexes were incubated *in vitro* with the RNase V1 and buffer, and the article reports that the deoxy substitutions reduced cleavage by RNase V1. No other ribonucleases were present during the RNase V1 reactions.

The Wyatt article also describes experiments designed to determine the structural requirements for E. coli RNase H. The experiments utilized 14-mer oligoribonucleotides with or without one or two 2'-deoxyribonucleotide substitutions hybridized to complementary 17-mer

deoxyoligoribonucleotides or hybridized to complementary 17-mer oligoribonucleotides having one or two 2'-deoxyribonucleotide substitutions. In the RNase H reactions, the substrates were incubated *in vitro* with RNase H and buffer, and the reactions did not contain any other ribonucleases. The article indicates that deoxy substitutions in the RNA strand of the RNA:DNA hybrids inhibited cleavage by RNase H. Significantly, the Wyatt article provides no teaching or suggestion that would have prompted those skilled in the art to produce oligonucleotide duplexes in which the first oligonucleotide is a gapmer having 2'-modified wings and the second oligonucleotide comprises at least one 2'-sugar modification. Nothing about the design or nature of the experiments described in the Wyatt article would have provided a reason to introduce sugar-modified nucleosides into both strands of an oligonucleotide duplex.

The remaining references fail to supply this missing teaching or suggestion, and thus fail to compensate for the deficiencies of the Wyatt article. As discussed at length previously during prosecution of this application, and as explained by Dr. Corey in his declaration, the description provided in the Manche article would not have prompted one of ordinary skill in the art to introduce 2'-sugar modifications into both strands of an oligonucleotide duplex. Instead, the Manche article describes short RNA duplexes that were used as substrates in experiments designed to elucidate the mechanism of activation of interferon-induced protein kinase DAI. Specifically, the experiments involved binding DAI to RNA duplexes of 15, 23, 34, 40, 55, 67, 85, or 104 nucleotides *in vitro*. The RNA duplexes were not chemically modified, and as pointed out by Dr. Corey in his declaration, nothing about the nature or aim of the experiments described in the Manche article provides any reason that would have prompted those of ordinary skill in the art to produce chemically modified RNA duplexes, much less duplexes having at least one sugar-modified nucleoside in both strands, as presently claimed.

The Monia article also fails to provide this missing teaching or suggestion. Instead, the Monia article describes 17-mer oligonucleotides having a central gap region of 2'-deoxynucleotides and having 5' and 3' wing regions of 2'- OCH_3 substituted nucleotides. These gapmers were hybridized to the following complementary RNAs:

1. A synthetic, end-labeled 25-mer RNA corresponding to Ha-ras RNA. The resulting duplex was used in *in vitro* melting experiments;

2. A 47-mer Ha-ras RNA hairpin. The resulting duplex was used in *in vitro* RNase activation experiments; and

3. Full-length Ha-ras mRNA, after introduction of the gapmer into HeLa cells that had been transfected with an Ha-ras expression plasmid, to determine the antisense activity of the gapmer.

The Monia article also describes hybridization of 11-mer, 13-mer, or 15-mer 2'-OCH_3 gapmers to end-labeled 25-mer RNAs corresponding to Ha-ras RNA. The resulting duplexes was used in *in vitro* melting experiments.

Finally, the Monia article describes melting experiments that utilized 17-mer gapmers having a central, 2'-deoxy region and 5' and 3' wing regions of either 2'-deoxy, 2'-O-pentyl, 2'-O-propyl, 2'-OCH_3, or 2'-fluoro groups hybridized to 25-mer RNAs corresponding to Ha-ras RNA. These gapmers were also introduced into HeLa cells that had been transfected with an Ha-ras expression plasmid to determine their antisense activity against full-length Ha-ras mRNA.

Significantly, the Monia article contains no teaching or description that would have prompted those of ordinary skill in the art to incorporate at least one modified sugar into both strands of an oligomeric compound duplex. The *in vitro* melting and RNase activation experiments described in the Monia article utilized duplexes in which only one strand contained chemical modifications, and there would have been no reason to utilize substrates having chemical modifications in both strands in such experiments. Furthermore, in the experiments in which the antisense activity of the single-stranded gapmers was analyzed, duplexes were not introduced into HeLa cells, but, rather, single-stranded gapmers were introduced, and their activity against unmodified, full-length mRNA target was determined. Accordingly, nothing about the design or objective of the experiments described in the Monia article would have prompted those of ordinary skill in the art to incorporate chemical modifications into both strands of an oligonucleotide duplex, much less incorporate 2'-modified wings into the first oligonucleotide and at least one 2'-sugar modification into the second oligonucleotide, as presently claimed.

Finally, the Shibahara application also fails to provide such a reason, but instead describes single-stranded antisense ribooligonucleotides targeted against HIV genomic RNA or against HIV DNA integrated into a chromosome. The Shibahara application describes experiments in which such single-stranded antisense ribooligonucleotides were introduced into cells that had been infected with HIV, and the cytopathic inhibitory effect of the ribooligonucleotides was determined. Although the Shibahara application describes chemical

modification of the antisense ribooligonucleotides, including 2'-OCH_3 modifications, the Shibahara application does not describe or suggest any reason to introduce chemical modifications into oligonucleotide duplexes.

Those of ordinary skill in the art would therefore have had no reason to produce duplexes of fully complementary oligonucleotides consisting of 17 to 25 linked nucleosides in which the first oligonucleotide is a gapmer having 2'-modified wings and the second oligonucleotide comprises at least one 2'-sugar modification before applicants' invention in view of the description provided in the cited references, when considered in combination in view of the state of the art at that time. The claimed oligonucleotides therefore would not have been obvious before applicants' invention.

The examiner asserts, however, that those skilled in the art would have introduced 2'-OCH_3 modifications into both strands of oligonucleotide duplexes used for testing "as substrates for various dsRNases" to protect the oligonucleotide duplexes from "unintended nuclease degradation." Contrary to the examiner's assertion, those of ordinary skill would not have had a reason to incorporate chemical modifications, such as 2'-sugar modifications, into both strands of oligonucleotide duplexs used as dsRNAse substrates at the time of the invention because the experiments described in the cited references do not involve conditions in which undesired nucleolytic degradation of such duplexes could have occurred. In the *in vitro* experiments described in the references, such as the RNase H and RNase V1 digestion experiments, in accordance with the experimental designs used, undesired nucleases were not present during the reactions that could have potentially degraded the substrates. As discussed above, only the RNase H and RNase V1 endonucleases were present in the reaction mixtures, and no other enzymes were present. Furthermore, in the experiments in which nucleic acids were introduced into cells or were treated with cellular extracts, single-stranded oligonucleotides targeted against full-length mRNAs or genomic RNAs were used in such experiments, and double-stranded duplexes were not utilized. None of the references therefore describes experiments in which double-stranded nucleic acids were introduced into an environment in which undesired nucleolytic degradation of the duplexes could have occurred. Accordingly, contrary to the examiner's assertion, the cited references fail to provide any reason that would have prompted those of ordinary skill in the art to protect both strands of an oligonucleotide duplex of the length claimed against nucleolytic degradation by introducing chemical modifications into both strands

of such duplexes. Dr. Corey explained that such compounds would not have been particularly suitable for the research described in the previously cited references, including the Manche article. Likewise, there would have been no reason why one skilled in the art would have used such compounds for the research described in the additional, newly-cited references. Because none of the cited reference, nor all of them combined, describe research for which one skilled in the art would have had a reason to make the claimed oligonucleotides, such compounds would not have been obvious at the time of the invention.

b. The examiner errs by ignoring record evidence of non-obviousness

While it is believed that the applied references do not establish a *prima facie* case of obviousness, in the event in may be considered that they do so, the examiner has ignored record evidence relevant to the present obviousness determination, *i.e.*, the Declaration of David Corey executed August 5, 2009. As mentioned, Dr. Corey's declaration was first presented in response to a previous obviousness rejection that was withdrawn in lieu of the present obviousness rejection. However, to the extent Dr. Corey discusses Manche and Baracchini; the declaration must be considered by the examiner. As stated in *In re Hedges*, 783 F.2d 1038, 1039 (Fed. Cir. 1986):

> If a *prima facie* case is made in the first instance, and if the applicant comes forward with reasonable rebuttal, whether buttressed by experiment, prior art references, or argument, the entire merits of the matter are to be reweighed. *In re Piasecki*, 745 F.2d 1468, 1472 (Fed. Cir. 1984).

Dr. Corey explains that Manche teaches away from the present composition as it provides no reason (1) to use a duplex having less than 33 base pairs (Corey Decl. at ¶ 16), (2) no reason to provide 100% complementarity (Corey Decl. at ¶ 17) and (3) no reason to make chemically modified oligonucleotides as the duplexes of the reference were "synthesized enzymatically, not through chemical synthesis and do not contain any chemical modification" (Corey Decl. at ¶ 18). Dr. Corey concluded that Manche "would not have prompted on to make the claimed compounds and that the claimed compounds would have been unsuitable for use in the research described in Manche. Corey Decl. at ¶ 19. Dr. Corey also provides a detailed analysis of Baracchini and explains why that reference does not teach or suggest the claimed compounds. Corey Decl. at ¶¶ 20-24.

c. The applied reference teach away from their combination as proposed by the examiner

It is axiomatic that a "prior [art reference] must be considered in its entirety, i.e., as a whole, including portions that would lead away from the invention in suit." *Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1561, 1568 (Fed.Cir.1987). Here the examiner has failed to consider those portions of the applied references that lead away from the claimed compositions. Dr. Corey explains in his declaration how Manche and Baracchini teach away from combining their teachings in the manner proposed by the examiner. Therefore, Dr. Corey's declaration provides strong evidence that the pending obviousness rejection is based upon impermissible hindsight instead of the teachings of the references themselves.

d. The examiner's rejection is made of whole cloth

The examiner's conclusion of obviousness is made from whole cloth and as a consequence falls from its own weight. Rather than identify a prior art duplex and explain how it would have been obvious to modify the prior art duplex to arrive at the claimed subject matter, the examiner constructs a duplex nowhere suggested by the applied references. For example, the examiner first concludes:

> It would have been obvious to one of ordinary skill in the art at the time the invention was made to make synthetic ribonuclease substrates wherein the substrate is an artificial duplex of a target RNA and a 2'-OMe-nucleotide-containing oligonucleotide because it was well known by those of skill in the art to study enzymes with such artificial substrates.

Office action of July 14, 2010 at 6. As is apparent, the examiner does not identify a specific prior art duplex. The examiner next concludes:

> It would have been obvious to use an artificial duplex of a target RNA and a 2'-OMe-nucleotide/RNA gapmer because Shibahara, et al. teach that 2'-OMe-nucleotide/RNA oligonucleotides are an improvement over DNA antisense oligonucleotides and because

> Monia, et al. teach antisense oligonucleotides having 2'-OMe-nucleotide/DNA oligonucleotides.

Id. at 6-7. Without identification of a specific prior art duplex to be modified, it is difficult to provide an informed response to the examiner's proposed modifications of the unidentified duplex. Before it can be said to have been obvious to modify a given duplex, the identity and properties of that complex must be known.

The examiner appears to recognize the frailties of the proposed combination as she proceeds to use an improper standard of obviousness, stating:

> One of skill ***could*** substitute RNA for DNA in the gapmer of Monia, et al. and would be motivated to do so to study the mechanism of action of the 2'-OMe-nucleotide/RNA antisense oligonucleotide of Shibahara, et al., such as by testing the duplexes as substrates for various dsRNases, while protecting the oligonucleotide from exonucleases.

Id. at 7 (emphasis added). The fact that one could rearrange a prior art product to meet a claimed product does not mean that it would have been obvious within the meaning of the statute to do so. *In re Gordon*, 733 F.2d 900, 902 (Fed. Cir 1984) (citations omitted) ("The mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification."). Here, the examiner's error is more glaring than that of the Gordon examiner since, contrary to the present examiner, the Gordon examiner relied upon a specific prior art device and provided an explanation of how one could have proceeded to modify that device to arrive at the claimed device.

The remainder of the examiner's conclusion of obviousness similarly lacks specificity as to how a prior art duplex is to be modified. When the examiner's conclusion of obviousness is read as a whole it is seen that the only reason that the disparate teachings of the applied references have been combined is the present disclosure and claims, *i.e.*, impermissible hindsight.

8. CONCLUSION

For at least the reasons discussed above, appellants respectfully ask the Board to reverse the examiner's rejection of the pending claims under 35 U.S.C. § 103(a).

Respectfully submitted,

DATE: April 30, 2012

/John A. Harrelson, Jr./

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9. CLAIMS APPENDIX

1-119 (canceled).

120. A composition comprising a duplex consisting of a first chemically synthesized oligonucleotide and a second chemically synthesized oligonucleotide, wherein:

each of the first chemically synthesized oligonucleotide and the second chemically synthesized oligonucleotide independently consists of 17 to 25 linked nucleosides, each nucleoside comprising a nucleobase and a sugar;

the first chemically synthesized oligonucleotide is 100% complementary to the second chemically synthesized oligonucleotide and to a target mRNA;

the first chemically synthesized oligonucleotide and the second chemically synthesized oligonucleotide are not covalently linked to each other; and

the first chemically synthesized oligonucleotide is a gapmer, wherein the gap comprises at least 4 nucleosides, each comprising a 2'-hydroxy-pentofuranosyl sugar moiety, and wherein each nucleoside of each wing comprises a 2'-sugar modification; and

the second chemically synthesized oligonucleotide comprises at least one nucleoside that comprises a 2'-sugar modification.

121. The composition of claim 120, wherein the second chemically synthesized oligonucleotide is a gapmer, wherein the gap comprises at least 4 nucleosides, each comprising a 2'-hydroxyl pentofuranosyl sugar moiety, and wherein each nucleoside of each wing comprises a 2' modification.

123 (canceled).

124. The composition of claim 120, wherein each nucleoside of at least one of the wings of the gapmer comprises a 2' sugar modification selected from fluoro, alkoxy, amino-alkoxy, allyloxy, imidazolylalkoxy, and methoxyethoxy.

125-126 (canceled).

127. The composition of claim 120, wherein each nucleoside of the 3' wing of the gapmer comprises a 2'- OCH_3.

128-135 (canceled).

136. The composition of claim 120, wherein each wing of the gapmer is from two to seven nucleosides in length.

137. The composition of claim 120, wherein at least one of the first chemically synthesized oligonucleotide and the second chemically synthesized oligonucleotide comprises at least one phosphorothioate linkage.

138. The composition of claim 137, wherein each of the first chemically synthesized oligonucleotide and the second chemically synthesized oligonucleotide comprises at least one phosphorothioate linkage.

139-167 (canceled).

10. EVIDENCE APPENDIX

A copy of the Declaration of Dr. David Corey filed under 37 CFR § 1.132 is attached to this Appeal Brief.

11. RELATED PROCEEDINGS APPENDIX

As discussed above, notices of appeal were filed for copending U.S. patent application numbers 10/701,264 (appeal brief filed March 22, 2012), 10/701,236 (appeal brief filed April 5, 2012), 11/054,848 (appeal brief filed April 30, 2010), 10/701,007 (appeal brief filed April 28, 2010), and 10/860,265 (appeal brief filed April 30, 2010), the claims of which are directed to compositions that comprise certain double stranded oligomeric compounds and to methods that utilize such compositions.